The Italian Meta-Analysis MISA and Causal Inference on the Short-Term Effects of air Pollution

Dalla metanalisi italiana MISA all'inferenza causale sugli effetti acuti dell'inquinamento atmosferico

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Riassunto: La maggior parte degli studi sugli effetti acuti dell'inquinamento atmosferico è basata sull'analisi delle serie temporali di inquinanti ed esiti sanitari. In Italia, sono stati effettuate due indagini di questo tipo, MISA1 e MISA2.

Questo lavoro, prendendo come riferimento i risultati dello studio MISA2, si propone di dare una risposta a tre aspetti molto rilevanti per l'interpretazione dei risultati derivanti da analisi di questo tipo: i. su quali basi sia possibile fondare il processo di inferenza causale nell'interpretazione dell'associazione di breve periodo fra indicatori di inquinamento ambientale ed esiti sanitari, ii. in quale misura i singoli inquinanti atmosferici siano da considerarsi pericolosi per la salute umana; iii. quanto siano affidabili le stime del rischio.

Keywords: causal inference, meta-analysis, air pollution, short term effects.

1. Introduction

Most studies on acute effects of air pollution used the time series approach, i.e. a single-group research design in which measurements are made at several different times, thereby allowing trends to be detected (Last 2001). This type of analysis examines changes in a given health outcome over time within a specific area as air pollution levels fluctuate. Investigations have taken advantage of the availability of routinely collected statistics both on the concentration of air pollutants and on health-related outcomes (such as death from any cause, death from respiratory or cardiovascular diseases, hospital admissions for respiratory or cardiovascular conditions). On this basis, the relationship between indicators of air quality in a given day and health-related effects in the following days can been assessed and quantified. Cities have been the target of most studies, and results of multi-city meta-analyses carried out in different parts of the world have been available since more than a quarter of century. Major investigations in the field are the NMMAPS (National Mortality, Morbidity and Air Pollution Studies) study on the 20 largest metropolitan areas in the US (HEI 2003) and the two APHEA (Air Pollution and Health, a European Approach) studies. APHEA 2 covered 29 European cities, for a total population of 43 million people (Katsouyanni *et al.* 2001). NMMAPS was reanalyzed because the original analysis had not taken adequately in consideration the control of confounding produced by temporal trends over the long period, by seasonal factors and climate. Such

reanalysis led to a moderate reduction of the estimate of the effect, but the sign of the association did not change.

The two MISA (Metanalisi italiana degli Studi sugli effetti a breve termine dell'inquinamento Atmosferico, Italian meta-analysis of studies on the short-term effects of air pollution) studies have been the major Italian time series meta-analyses: MISA. 1 (Biggeri *et al.* 2001, Biggeri *et al.* 2003, Biggeri *et al.* 2005) covered data from 8 Italian cities (Bologna, Firenze, Milano, Palermo, Ravenna, Roma, Torino and Verona) during the 90s, whereas the more recent MISA 2 (Biggeri *et al*. 2004) .included data from 15 Italian cities (the same as above plus Catania, Genova, Mestre-Venezia, Napoli, Pisa, Taranto and Trieste) at the turn of the millennium. Air pollutants considered in the two MISA as well as in most other analyses were sulphur dioxide (S02), nitrogen oxide (NO2), carbon monoxide (C0), ozone (O3) and suspended particulate matter (SPM) and/or its fractions.

The present contribution is focussed on the results of MISA 2 and addresses three major issues: i. robustness of the causal inferential process in the interpretation of the association between indicators of air pollution and short-term health related outcomes; ii. the extent to which specific air pollutants can be considered as hazardous for human health and iii. the reliability of risk estimates.

In the present context, reference will be made only to the meta-analytic estimates. Factors influencing city-specific findings are both methodological (a different degree of imprecision in exposure estimates) and factual. In both MISA 1 and MISA 2 the effects of PM10 were estimated to be greater in cities located south in the Italian peninsula (which might reflect a different degree of interaction with meteorological factors as well as a different lifestyle). However, additional investigations are required in order to understand the reasons of the high heterogeneity variance estimates of the MISA studies.

2. Causal inference

Throughout the scientific literature, the health-related outcome for which the available data are most abundant is the whole group of early deaths from natural causes (International Classification of Disease, ICD-IX 0-799): this will be the main focus of the present contribution. Given the route of exposure and current knowledge on the mechanisms of toxicity of air pollutants, an effect on mortality for circulatory or respiratory diseases (respectively ICD-IX 390-459 and ICD-IX 460-519) may reflect a more specific association (which nevertheless might be difficult to identify because of a lower statistical power). The MISA studies, as well as many previous studies, also analyzed the association with hospital admissions for respiratory, cardiovascular and cerebrovascular diseases. As a proxy to effects, hospital admissions may not be as reliable as mortality statistics. Although in recent years the quality of the files of admissions for acute conditions is believed to be good, the homogeneity of quality across Italian regions has not been thoroughly assessed. In addition, hospital admissions rely on the availability of beds, the offer of which may be restricted during the summer. In addition, it has been pointed out that deaths associated with air pollution also occur

outside hospital (Brunekreef and Holgate 2002),. Thus, as far as hospital admissions, reference will be made only to estimates providing supportive evidence to findings obtained in the analyses of mortality.

The criteria proposed by Austin Bradford Hill almost half a century ago (Hill 1965) have been pivotal for assessing causality in environmental epidemiology, including the case of air pollution and death. The following paragraphs intend to apply these criteria to the interpretation of the results of MISA.

Strength of the association: in most studies, including MISA 1 and MISA 2, the relationship has been estimated as percentage change in the outcome associated to a unit increment of the pollutant (10 µg/m3 for SO2, NO2, PM10 and Ozone and 1 mg/ m3 for CO). Compared with common observations in environmental epidemiology, these relative risks are very small. Overall MISA 2 associations with mortality related outcomes are reported in Table 1: fifteen out of 15 associations bear a positive sign, but only in 3 instances the lower limit of the interval of credibility is greater than zero. The latter are the associations between NO2 and total mortality, CO and total mortality and PM10 and mortality from cardiovascular diseases. The former two associations are supported by a statistically significant association between the relevant pollutant and hospital admissions for respiratory and cardiac conditions (percent increase in risk respectively 0.77 and 0.57 for NO2 and 1.25 and 1.44 for CO). . The association between PM10 and heart diseases is consistent with an association with hospital admissions for cardiovascular conditions of borderline statistical significance (percent increase 0.29, 95% CrI -0.04 to 0.59) and a statistically significant association with hospital admissions for respiratory conditions (percent increase in risk 0.60).

Table 1: *Overall effect estimates and 95% credibility interval (95% Cr I) of each air pollutant on mortality in 15 Italian cities 1996-2002.. The effects are expressed as percent increase in risk by 10 µg/ m^3 (1 mg for CO) increase in pollutant concentration. Lag 0-1 days (from ref 3)*

	All natural deaths		Deaths from respiratory conditions		Deaths from cardiovascular conditions	
	effect	95% CrI	% change	95% CrI	% change	95% CrI
SO2	0.60	-0.39 to 1.59	1.55	-2.22 to 5.38	1.11	-0.64 to 3.12
NO2	0.59	0.26 to 0.94	0.38	-0.63 to 1.74	0.40	-0.46 to 1.05
CO	1.19	0.61 to 1.72	0.66	-1.46 to 2.88	0.93	-0.10 to 1.77
PM10	0.31	-0.19 to 0.74	0.54	-0.91 to 1.74	0.54	0.02 to 1.02
Ozone *	0.27	- 0.26 to 0.70	0-01	-1.67 to 1.30	0.22	- 0.33 to 0.70

* only during between May 1-September 30

Temporal relationship: this *sine qua non* criterion is fulfilled in MISA as well as in all other studies based on temporal series. In most studies, a consistent effect on mortality for all natural causes has been identified when a lag of 0-1 days was adopted. The greatest effects on hospital admissions were observed in relation to the average atmospheric concentrations during the 3 preceding days.

External consistency: (i.e.replication of results in studies in different settings using different methods). Indeed, not only MISA 1 and 2 have confirmed findings obtained in many other studies but the great bulk of the available literature clearly indicates the existence of an association between indicators of air pollution and mortality for natural causes (as well as for other end points). Within the major studies on the effects of air pollution, estimates of the effects on mortality of PM10 have been fairly consistent, keeping into account the different settings in which the relevant populations live (Table 2). Results have been somewhat less consistent for other pollutants.

Table 2: *Percent increase in risk of death from natural causes associated with a 10 µg/ m^3 increment in the average concentration of PM10 in air in three different studies (from ref 3)*

Study	% increment	Median PM10 concentration	Lag	period
MISA 2	0.31	46.2	0-1	1996-2002
APHEA	0.41	40.0	0-1	1990-1997
NMMAPS	0.19	27.1	1	1987-2000

Specificity: This criterion is established when a single putative cause produces a specific effect. This is not the case for the associations under study. There is agreement that for the time being all pollutants which have been investigated should be considered as no more than indicators of exposure. Also the investigated effects are far from being specific (i.e. exclusive and constant).

Dose-response relationship: (i.e. the observation that an increasing level of exposure increases the risk) . In the case of air pollution, assessing this criterion is problematic given that no single specific agent can be indicted to be responsible for all outcomes. Over the years, total suspended particulate (TSP) and later PM10 (and more recently PM2.5) have been considered to be the indicator of choice. As early as in a meta-analysis carried out in 1994 (Schwartz 1994) it was assessed that an increase of the daily average concentration of SP corresponded to an increase in of daily mortality from natural causes. This was confirmed in a variety of subsequent studies., although, admittedly, the exact shape of the dose-response relationship is yet to be determined.

Biological plausibility and coherence: the former concept implies that the association agrees with currently accepted understanding of pathobiological processes. The underlying rationale is weak: Bradford Hill himself emphasized that at any given time current knowledge on mechanisms of diseases simply reflects the amount of attention previously given to specific problems. Coherence implies that the association should be compatible with existing theory and knowledge. In general terms, given that inhalation is a major route of absorption of environmental pollutants, the association

between air pollutants and health is not surprising. Supportive evidence is brought about by the fact that effects of air pollution are somewhat greater among the very young and the very old. The association between PM10 and heart diseases might well find an explanation on recent observations that PM10 and other atmospheric pollutants may affect blood clotting (Pekkanen 2000). Although the experimental reproduction of the conditions of human is problematic, animal and in vitro experimental studies have demonstrated the powerful oxidant capacity of ozone. Also NO2 has the capacity of activating oxidant pathways, although to a lesser extent than ozone. Experimental studies with particulates have shown potent proinflammatory effects and activation of oxidant pathways as well as the generation of factors that influence blood clotting (see summary review in Brunekreef and Holgate 2002)

Confounding: a major advantage of the time series studies is that exposures that could potentially confound the association between air pollution and health (e.g. age, smoking habits, occupational exposure and diet) do not change over a short period. On the other hand, factors likely to vary with daily mortality are meteorological conditions and influenza epidemics. These have been taken into account in most time series studies, including MISA. Although some residual confounding cannot be ruled out, findings strongly suggest that the association between indicators of air pollution and health effects is likely to be real.

3. Which specific air pollutants can be considered as hazardous for human health?

There is a consensus of opinion that all of the individual pollutants for which associations with health outcomes have been identified ought to be considered primarily as markers of pollution. The collinearity between pollutants' concentrations is high (with the possible exception of ozone) and a role of some other unidentified pollutant correlated to measured pollutants' concentrations cannot be ruled out.

Estimates of the effects of SO2 are very imprecise. Current concentrations in Italian cities are below or close to the detection limits of the analytical methods.

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There are several reasons for considering that suspended particulate matter (SPM) has a major role in the noxiousness of air pollution. SPM is a mixture of particles of different size and state (solid/liquid) ranging from 0.01 μm to > 10 μm in diameter: particles measuring < 10 μm (PM10) penetrate into the lower respiratory system and the smallest ones (< 2.5 μm, PM 2.5) arrive at the gas-exchange level and might penetrate into the bloodstream. Particles may contain metals, such as zinc and nickel, organic materials and polycyclic aromatic hydrocarbons, some of which are carcinogenic. Black soot contributes up to 10% PM2.5. Major advances in analytical methods have taken place over the last few decades and the tendency nowadays is towards the measurement of PM2.5. Nevertheless, the application of such methods has not taken place with the same pace in different countries and areas, which may impair comparisons across studies. PM2.5 was not measured in Italy during the years covered by MISA, and criteria for measuring PM10 were not uniform over the country.

Most of the epidemiological studies undertaken during the 90s and in the new millennium have estimated effects on human health assuming that PM is a major pollutant of concern. For instance, estimates included in the WHO report on the 8 major Italian cities relied on the effects of PM only, although the report pointed out that "in many cases, PM may be serving as a surrogate measure for the complex mix of particles and gases that result from fuel combustion from automobiles or power generators" (Martuzzi *et al*. 2002).

In most instances models have been fitted with only one pollutant at a time. Results of multipollutant analysis are limited, problematic (because of the high collinearity between pollutants' concentration and the consequent statistical instability) and difficult to interpret.. MISA 2 has measured some effects of PM10 (on mortality from all natural causes, from respiratory conditions and from cardiovascular conditions) after adjustment for ozone and NO2. Whereas ozone seemed to confound to a very limited extent, the effects of PM10, adjustment for NO2 significantly reduced the estimate of the percentage increase of effects by an increment of 10 µg/m3 PM10. Remarkably enough, in the APHEA study, the PM10-associated 0.5% increased risk for mortality from cardiovascular conditions disappeared after adjustment for NO2 (Le Terre *et al*. 2002) Whereas these observations ought to be seen in the light of an overall consideration of data and of the limits of the methods used for adjustment, they cast some doubts on the relative importance of PM10 over NO2.

4. The reliability of risk estimates.

There may be uncertainty about the exclusion of non-linearity or thresholds in the concentration-response functions. The statistical power of the epidemiological studies is not sufficient for estimating effects at very low dose-levels (say, just above the detection limits of the analytical method) and therefore for determining the shape of the dose-response curve over the whole range of exposures. In the case of PM10, in one study in the US (Schwartz 2000), the percentage increase of deaths for an increment of 10 µg/ m3 PM 10 was measured limited to the days in which the mean concentrations of PM10 was lower than 50 µg/m3 . Indeed, the estimate was somewhat higher than the corresponding estimate in the whole series (respectively 0.67% (0-52-0.81) and 0.87% (0.62-1.12). Results of the metaregression analysis included in MISA suggest that the effects are somewhat more limited in the cities exhibiting higher average PM10 concentrations. These observations indicate that there is no threshold at current concentrations in Italian cities as well as the tendency to a plateau for very high doses.

In an analysis of data from 20 US cities, flexible modelling strategies were developed, including spline and threshold exposure-response models. The spline model showed a linear relation without indication of threshold for PM10 and relative risk of death for all causes and for cardiorespiratory causes. On the contrary, for other causes of death, the risk did not increase until approximately 50 µg/ m3 PM10. A previous analysis focussed on particulate matter in two US cities had estimated that the relationship with mortality was similar across all four quartiles of exposure (Schwartz and Dockery 1992 a and 1992 b) Thus, the assumption of linearity seems to be

acceptable, at least for PM10 and at least for the levels of concentrations which are typical of Italian cities.

In the Italian studies, the magnitude of the effect associated to PM10 is of the same order of magnitude of that estimated in the United States and elsewhere in Europe (Fig. 2). Indeed, the interaction with other factors (weather, time spent outdoor, smoking status, access to health care etc) may be different. A relevant observation of MISA 2 is that for all pollutants the percentage variations in mortality (and hospital admissions) associated with the increment in pollutants' concentration were significantly higher in summer than in winter. In the case of mortality from all natural causes, the percent increases in risk by unit increment in exposure to PM10, in winter and in summer were respectively: SO2: 0.55 and 1.21, NO2 0.23 and 1.66, CO 0.84 and 4.45, PM10 0.08 and 1.95. These huge differences cast some doubts on the fairness of the attribution of all of the effects to any specific pollutant.

A source of uncertainty is error in measuring exposure. In most studies, this is done on readings from nearby fixed-site monitors. Particularly in the case of PM, different methods have been used. Early studies (including some cities in MISA 1) measured total suspended particles (TSP) and estimated concentrations of PM10 through a conversion factor: although the latter was established through validation studies, the procedure limits the comparability of findings across studies. Comparability of findings between MISA 1 and MISA 2 is also impaired by the fact that the two studies did not always use the same fixed-site monitors. .

For the 15 cities included in MISA 2 and for the period covered by the study (1996-2002), the report (Biggeri *et al*. 2004) includes estimates of the annual number of deaths from natural causes attributable to concentrations of atmospheric pollutants in excess over the baseline and over the European limit values. Keeping into account all the uncertainties of this exercise, such a number is in the order of a few thousand.

Excess risk estimates ought to be seen in the light of a possible "harvesting" phenomenon. It can be hypothesized that if all the increase in the acute effect was due to persons belonging to a hypothetical high risk pool of susceptible persons, with no possibility of transition from the low risk to the high risk compartment, the pool would become thinner within a few days. This possibility can be investigated through the comparison of estimates of the association between the atmospheric concentration of pollutant and the risk for the outcomes using different lags. MISA has investigated this point. The percentage increase in mortality over a period of 15 days were 1.45 for SO2, 0.83 for NO2, 1.37 for CO, 0.32 for PM10 and - 0.09 for Ozone vs. corresponding estimates of 0.60. 0.59, 1.19. 0.31 and 0.27 in the analyses restricted to lag 0.1 days. Thus, it seems that there was no trend towards a decrease of mortality rates comparable to the increase taking place immediately after the pollution peak as one would expect on the assumption of a harvesting phenomenon. Findings on this phenomenon recorded in MISA largely correspond to those of studies carried out in the US . As mentioned above, it has been pointed out that many deaths associated with air pollution occur outside the hospital , which also supports the suggestion that these patients were often not terminally ill (Brunekreef and Holgate 2002)

Finally, MISA and other studies on temporal series are based on aggregated data, thus allowing for some sort of ecologic bias. The magnitude of the latter, if any, is likely to be small, given the consistency of findings, at least in terms of the sign of the association.

5. Conclusions

Remarkably enough, in the case of the short-term effects of air pollution, the replication of studies carried out with similar models in different contexts has led to a surprising consistency of findings. There is little doubt that the association of markers of air pollution and death exists and is causal. Particulate matters are likely to have a major, albeit non exclusive role. However, the relationships which have been demonstrated are not easy to interpret. Major controversial aspects to be addressed in the future remain:

- The precise role of each pollutant in the overall toxicity of "air pollution"
- The role of pollutants which are not routinely measured (e.g. benzene and other solvents),
- The validity of the indicators of exposure
- The meaning of mortality associated to air pollution in terms of reduction of life expectancy, incidence of specific diseases and exacerbation of pre-existing conditions
- The shape of the dose-response relationship
- The role of effect modifiers on the associations which have been observed
- The mechanism of action of toxic pollutants

6. References

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